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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/735,363 | 12/12/2000 | Nigel C. Phillips | 02811-0181 | 3925 |

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| EXAMINER | |
|---|---|
| ZARA, JANE J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/735,363 | PHILLIPS ET AL. | |
| | Examiner | Art Unit | |
| | Jane Zara | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,10,59,61,62,65-67 and 69-119* is/are pending in the application.

4a) Of the above claim(s) *84-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10,59,61,62,65-67 and 69-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office action is in response to the communication filed 12-23-05.

Claims 1, 10, 59, 61, 62, 65-67, 69-119 are pending in the instant application.

### *Election/Restrictions*

Newly submitted claims 84-119 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 84-119 are directed to methods of treatment, which is a non-elected invention (see restriction requirement mailed 1-4-02).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 84-119 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims 84-119, drawn to an invention nonelected with traverse in the election filed 3-13-02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Claim Objections*

The claims are drawn to compositions comprising synthetic phosphodiester nucleotides comprising 3'-OH and 5'-OH synthetic sequences of varying SEQ ID Nos.

In claim 1, line 1, the word "comprising" is interpreted as referring to the compositions, and the sequences are interpreted as consisting of the particular sequences recited.

***Response to Arguments and Amendments***

*Withdrawn Rejections*

Any rejections not repeated in this Office action are hereby withdrawn.

*New Rejections/Rejections Necessitated by Amendments*

Claims 1, 10, 59, 61, 62, 65-67, 69-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a subset of the sequences claimed to provide inhibition of cellular growth or other cellular effects in vitro, does not reasonably provide enablement for methods of treatment in vivo alone or in combination with a chemotherapeutic agent.

The claims are drawn to pharmaceutical compositions comprising SEQ ID Nos: 8-10, 25, 26, 41-43, 45 or 46 in combination with a chemotherapeutic agent. The sequences claimed range in size from trinucleotides to oligonucleotides comprising 6 or 9 nucleotides.

**The state of the prior art and the predictability or unpredictability of the art.** Branch and Crooke teach that the in vivo (whole organism) application of nucleic acid molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules or alteration of target cells. (See entire text of A.

Branch, Trends in Biochem. Sci., 23, 45-50, 1998; and S. Crooke, Antisense Res. & Application, Chapter 1, pages 1-50, ed. by S. Crooke, Springer-Verlag, especially pages 34-36).

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy using nucleic acid molecules for expressing a polypeptide and for inhibiting the expression of a polypeptide using antisense oligonucleotides: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release... remains one of the major hurdles in the field." ((See Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51).

Cellular uptake by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of small molecules in vitro and in vivo (see Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80; see Chirila et al, Biomaterials, Vol. 23, pages 321-342, 2002, especially pages 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic molecules to target cells).

**The amount of direction or guidance presented in the specification AND the presence or absence of working examples.** The specification teaches a number of nucleic acid sequences and their effect on the growth and various cellular processes in vitro. Applicants have not provided adequate guidance in the specification toward a method of providing treatment effects using the various oligonucleotides claimed alone or in combination with a representative number of chemotherapeutic agents, including using a representative number of species of antimetabolites, alkylating agents or hormone antagonists. Applicants have not provided adequate guidance for providing treatment effects using the various oligonucleotides claimed in any animal following the administration of the oligonucleotides alone or in combination with a chemotherapeutic agent in an animal. One skilled in the art would not accept on its face the examples given in the specification of in vitro results on cell growth or other cellular processes using a subset of the oligonucleotides claimed as being correlative or representative of the ability to provide treatment effects in a subject following administration the oligonucleotides alone or in combination with chemotherapeutic agents as instantly claimed. There is a lack of guidance in the specification and an unpredictability associated with the successful targeting and delivery of nucleic acids or other molecules to appropriate target cells in an organism, alone or in combination with a representative number of chemotherapeutic agents, whereby treatment effects are provided in an organism.

**The breadth of the claims and the quantity of experimentation required.** The claims are drawn to pharmaceutical compositions comprising SEQ ID Nos: 8-10,

25, 26, 41-43, 45 or 46 in combination with a chemotherapeutic agent. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of species of the genera antimetabolites, alkylating agents or hormone antagonists in combination with the various oligonucleotides claimed to provide treatment effects in an animal. Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism, whereby the compound or compounds claimed are effectively delivered in adequate quantities to the target cells, and treatment effects are provided for each oligonucleotide claimed. Since the specification fails to provide sufficient guidance for the methods or the broad genera of compounds claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Jane Zara**
**3-3-06**

JANE ZARA, PH.D.
PRIMARY EXAMINER

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